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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/741,550	12/19/2000	Julia Y. Ljubimova	18810-80364	6437

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/741,550	LJUBIMOVA ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,13-18,21-29,32-36,44,45,48-68 and 75-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,13-18,21-29,32-36,44,45,48-68 and 75-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☑ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed November 17, 2003 and correspondence filed February 6, 2003. Currently, claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-68, 75-78 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the claims and the arguments.

Claim Rejections - 35 USC § 112-Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-68, 75-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to methods for detecting any malignant tumor in a human subject by comparing the expression level of laminin alpha4-specific mRNA to

normal controls, wherein overexpression of laminin alpha4-specific mRNA indicates the presence of a malignant tumor.

The claims are very broadly drawn to detecting a laminin alpha4-specific mRNA. The specification specifically states that laminin alpha4 specific polynucleotide sequence include mRNA sequence at least 5-30 contiguous nucleotides long, and preferably at least about 45 contiguous nucleotides long. A laminin alpha4 specific mRNA can be but is not necessarily an mRNA species containing a nucleotide sequence that encodes a functional laminin alpha4 subunit or a fragment thereof. Also, included among laminin alpha4 specific mRNAs are splice variants" (page 20, lines 10-20). This extremely large genus of nucleic acids has not been provided in the instant specification or the art at the time the invention was made. Further, the specification fails to provide evidence that splice-variants, mutations, homologs and other variations of the laminin alpha4 specific mRNAs are associated with malignant tumors. The art teaches mutations or splice variants in genes may significantly alter the expression patterns of genes such that they are no longer commensurate in expression with the wild type gene. It is unpredictable that the skilled artisan could use the murine homolog of laminin alpha4 to detect tumors in humans. There is no evidence that homologs would have significant homology to detect and diagnose tumors. Based upon the evidence in the specification, the declaration and the post filing date art, detection of laminin-9 does not appear to be predictably associated with tumors.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, Applicant has defined only single Genbank Accession Number provided in the art. It is noted that Genbank Accession Numbers change over time, so in the event that applicant wished to bring the Genbank Accession Number into the claims or the sequence listing, appropriate documentation of the sequence at the time of filing would be required. As discussed above, the very broad genus of alpha4-specifc mRNA sequences has not been described because neither the specification nor the art teaches a representative number of mutations, homologs, splice variants which

are encompassed by the genus. Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Claim Rejections - 35 USC § 112- Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-68, 75-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting a glioma in a human subject by detecting quantitatively or semi-quantitatively a level of expression of laminin alpha4 mRNA or protein of Genbank Accession Number Z99289, does not reasonably provide enablement for detecting any malignant tumor, including breast and prostate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are broadly drawn to methods for detecting <u>any</u> malignant tumor in a human subject by comparing the expression level of laminin alpha4-specific mRNA to normal controls, wherein overexpression of laminin alpha4-specific mRNA indicates the presence of a malignant tumor.

The art, namely Ringelmann et al. (Experimental Cell Research, Vol. 246, pages 165-182, 1999) teaches strong interstitial expression of laminin alpha4 mRNA in

myogenic tissues of embryonic but not mature mice, implicating a role for this laminin alpha chain in myogenesis (page 166, col. 2). Additionally, Previtali et al. (Glia, Vol. 26, pages 55-63, 1999) teaches the abnormal expression of a laminin receptor, alpha6beta4 integrin in human astrocytomas (abstract). Tysnes et al. (Int. J. Devl. Neuroscience, Vol. 17, No. 5-6, pages 531-539, 1999) teaches "compared to normal astrocytes, neoplastic astrocytes in situ have shown increased expression of the laminin receptor alpha3 and beta1 integrin subunits" (page 538).

Ljubimova et al. (Cancer Research, Vol. 61, No. 14, pp 5601-5610, July 2001) teaches that lamini-8 and lamini-9 have different effects on the recurrence of tumors. Thus, it is clear that mere detection of alpha4, without more does not accurately provide an analysis of recurrence rates.

The claims are very broadly drawn to detecting a laminin alpha4-specific mRNA. The specification specifically states that laminin alpha4 specific polynucleotide sequence include mRNA sequence at least 5-30 contiguous nucleotides long, and preferably at least about 45 contiguous nucleotides long. A laminin alpha4 specific mRNA can be but is not necessarily an mRNA species containing a nucleotide sequence that encodes a functional laminin alpha4 subunit or a fragment thereof. Also, included among laminin alpha4 specific mRNAs are splice variants" (page 20, lines 10-20). This extremely large genus of nucleic acids has not been provided in the instant specification or the art at the time the invention was made. Further, the specification fails to provide evidence that splice-variants, mutations, homologs and other variations of the laminin alpha4 specific mRNAs are associated with malignant tumors. The art

teaches mutations or splice variants in genes may significantly alter the expression patterns of genes such that they are no longer commensurate in expression with the wild type gene. It is unpredictable that the skilled artisan could use the murine homolog of laminin alpha4 to detect tumors in humans. There is no evidence that homologs would have significant homology to detect and diagnose tumors. In the instant case, Applicant has defined only single Genbank Accession Number provided in the art. It is noted that Genbank Accession Numbers change over time, so in the event that applicant wished to bring the Genbank Accession Number into the claims or the sequence listing, appropriate documentation of the sequence at the time of filing would be required. Based upon the evidence in the specification, the declaration and the post filing date art, detection of laminin-9 does not appear to be predictably associated with tumors.

With respect to Claims 28-29, 32-36, 44-45, 48-59 the post filing date are suggests that laminin-8 which was expressed mainly in blood vessel walls of GBMs and histologically normal tissues adjacent to GBMs had a shorter mean time to recurrence. Whereas lamini-9 which was expressed mainly in blood vessel walls of low-grad tumors and normal brain, had a greater time to tumor recurrence. Moreover, the specification, on pages 44-54 discuss Patient 16 and 39 and the relative recurrence rates. It is noted that claims 44 and 53 are sufficiently identical.

With respect to Claims 60-66 directed to method of classifying the grade of a malignant tumor by comparing expression profiles, the specification has provided no guidance to classification. The specification has provided no guidance as to what the

"relatively high invasiveness of the tumor" encompasses. The specification seems to illustrate a few examples where laminin alpha4 is overexpressed in astrocytoma grade II. The specification teaches that astrocytoma grade II is a lower grade malignant tumor (page 11, lines 15-16). Therefore, it is unclear how the overexpression of laminin is indicative of relatively high invasiveness of the tumor. The claims does not appear to make any distinction between low grade and higher grade tumors. Therefore, it is unclear how the tumors are classified. While the skilled artisan could provide further undue experimentation to determine a value for expression in the various types of tumors and obtain thresholds for classifying the tumors, the instant specification does not provide any predictive correlation between thresholds and classifications of tumors into grades, as required by the claims.

Moreover, the specification provides no guidance to the skilled artisan how to use the invention with respect to any type of malignant tumor. The specification does not teach expression levels in all malignant tumors, including breast, prostate, lung, colon, skin, etc. While one could conduct additional experimentation to determine whether, e.g., overexpression of laminin alpha4 might be associated with, e.g., additional malignant tumors, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue. In the absence of guidance from the specification, one skill in the art may look to the teachings of the prior art for enablement of a claimed invention. However, the closest prior art references, do not provide support for the use of laminin alpha4 expression as an indicator of malignant tumor. Thus it is unpredictable as to whether one could successfully use the

claimed invention, and given the fact that neither the specification nor the prior art provide evidence of a correlation or association between laminin alpha4 expression and malignant tumors, it is further unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention. Accordingly, it would require undue experimentation for a skilled artisan to use the claimed invention.

Response to Arguments and Declaration

The response traverses the rejection.

First, as correctly questioned by the applicant, the enablement rejection is a scope of enablement rejection where Claims 18, 21-27 have been deemed enabled based upon the teachings in the specification at the time the invention was made. As stated previously, upon review of the remarks and the specification, the level of expression in laminin alpha4 mRNA and protein appear to be correlative with gliomas (see Figure 5 and Table 7). Each of these showings demonstrate that there is differential expression between gliomas and normal tissues. Therefore, claims drawn to gliomas would be enabled.

On page 21 of the response filed November 17, 2003, the response asserts that there is no evidence that the B1 subunit drives or controls the expression of the alpha4 subunit. This argument has been thoroughly reviewed, but is not found persuasive because the evidence provided in the declaration, the specification and the post-filing date art appears to suggest that laminin-8 and laminin-9 do not act in concert with each other an appear to have different diagnostics.

As discussed previously, the Declaration states that "like brain malignancies, malignant tumors of the breast overexpress alpha4 laminin." (page 2 of Declaration filed March 24, 2003). The specification makes clear that the laminin alpha4 subunit is particular to laminin-8, laminin-9 and laminin-14 (page 5, lines 17-19). The data in the Declaration illustrates that Laminin-8 is not expressed in normal tissue, but appears expressed in invasive carcinoma, metastases of invasive carcinoma and non-invasive carcinomas. However, Laminin-9 does not appear to be correlative of the same expression pattern. Laminin-9 is expressed in normal breast tissue (40%). This appears to indicate that the alpha4 subunit may not be responsible for the expression in breast tissues. The response argues on page 23 of the Response that "Laminin 8 requires an overexpression of both alpha4 and beta1 subunits." Therefore, the expression of Laminin 8 in breast, but not in normal may be due to the beta1 subunits since Laminin 9 does not have the same correlation.

The response asserts that the declaration clearly shows that the invention is readily applicable to breast cancer as well as brain cancer (page 22 of response). This argument has been thoroughly reviewed, but is not found persuasive because the Declaration illustrates the expression of brain metastasis of breast cancer. As stated in the prior office action, "with regard to the data presented on Page 4 of the Declaration, the western blot appears to show a lack of laminin alpha4 chain expression in normal breast tissue and its strong expression in breast cancer metastases. The Figure illustrates that the metastasis are "brain metastasis of breast cancer." Therefore, the results of the Figure appear to support a brain metastasis of breast cancer, but does not

support breast cancer malignancies. As stated previously, while one could conduct additional experimentation to determine whether, e.g., overexpression of laminin alpha4 might be associated with, e.g., additional malignant tumors, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue." This showing of expression in alpha4 chain does not appear to be indicative of breast cancer, but rather brain cancer which has metastasized. It is well established that different cancers have expression of different genes. Thus, there is no indication that breast cancer, or any other cancer, has increased expression of alpha4 chain. The response appears to support this conclusion by asserting that "very high levels of alpha4 and the presence of laminin 8 are makers for an aggressive tumor that has a very high potential for metastasis." Thus, the evidence provided in the declaration may support that metastasized tumors from the brain also show an increased level of alpha4, however they do not illustrate that alpha4 is overexpressed in breast cancer.

While the Declaration asserts, "My studies show that prostate malignancies, like those of the brain and the breast also overexpress alpha4 laminin." (Page 3 of the Declaration filed March 24, 2003). This statement is confusing because while the brain malignancies appear to be associated with alpha4 laminin, the data provided in the Declaration do not appear to support the overexpression of alpha4 laminin in breast malignancies. Therefore, without further information and data, the examiner is unable to evaluate the data regarding prostate malignancies.

With respect to Claims 60-66, the response argues that directed to method of classifying the grade of a malignant tumor by comparing expression profiles, the specification has provided no guidance to classification. First, the claims require "at least one specific to a growth factor-related gene or to a structural gene other than a laminin gene." The response appears to asserts that the claim is directed to beta1 subunits because the response state "this being the other overexpressed structural gene." Therefore, the response does not appear to be arguing what is claimed.

The response (page 24 of response filed November 17, 2003) asserts that traditional ranking or grading of tumors is based strictly on histological features but histological features were unable to correctly identify aggressiveness and tendency to recur. The Examiner pointed out several points of confusion and the response asserted that this was exactly the point. However, there is no evidence that the expression patterns provide a more accurate measurement than the art established histological methods which have existed for many years and are well established. The method merely describes a generic method for assessing grades such that the higher the expression the higher the grade. The response appears to be arguing that the instant application has determined a system that "is intended to replace the traditional histological grading or ranking." This aspect of the instant invention does not appear to have been fully developed. It is noted that overexpression in particular tissues may be indicative of tumors, however there is no apparent thresholds for assigning any particular rank. In the event that overexpression of 2x as compared to normal is ascertained, there is no guidance as to what rank or grade tumor is found. The

specification does not appear to establish any ranking system, any system for tumor aggressiveness. There are not specifics in the description what various grades of tumors encompass. Therefore, the skilled artisan would not be able to establish the specific grade of a tumor with out further experimentation.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

6. No claims allowable.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 6:00 a.m. to 3:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (571) 272-0507

J. Goldberg

Jeanine Goldberg
Patent Examiner
February 9, 2004